Lecture Notes: Antimicrobial peptides (Janet Deane)

Antimicrobial peptides (AMPs, also known as Host defence peptides HDPs) form part of the innate immune system. AMPs are naturally occurring antibiotics produced by all living organisms – including bacteria themselves. They are directly cytotoxic to microbes and also act as immunomodulators to recruit cells of the adaptive immune system.

AMPs are small peptides (12-50 amino acids) composed of hydrophobic and positively charged residues. They are classified based on their structure, amino acid composition and number of disulfide bonds.

There are two main families of AMPs: defensins and cathelicidins. Defensins form β-strand secondary structure and are stabilised by 3 disulfide bridges, while cathelicidins are α-helical.

AMPs are produced by epithelial cells of mucosal surfaces such as the skin, gastroinstestinal and respiratory tracts. They are also produced by granule-containing leukocytes such as neutrophils and cytotoxic T lymphocytes.

AMPs primarily kill microbes by membrane permeabilisation. AMPs interact with membranes by being amphipathic (hydrophilic residues on one side and hydrophobic on the opposite face). The hydrophobic residues can insert into and destabilise membranes (Fig.1A). The peptides are also thought to insert into membranes to form transmembrane pores (Fig. 1B). Membrane permeabilisation is thought to be the primary mode by which AMPs kill microbes. However, there is some evidence to suggest that they play additional roles in microbial killing by interfering with cellular processes.

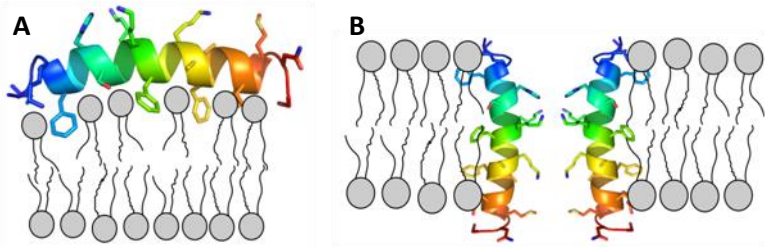

Fig. 1. Models for membrane permeabilisation by amphipathic AMPs. **A.** Carpet model. **B.** Transmembrane pore model.

AMPs kill a wide range of microbes and their specificity is primarily determined by electrostatic complementarity between the positively charged AMPs and negatively charged components of bacterial membranes.

Some cells produce AMPs constitutively while others only release AMPs upon appropriate triggers such as cytokines and microbial components. AMPs are often stored in secretory granules and released at mucosal surfaces or sites of infection.

AMPs are often produced as inactive precursor proteins that require cleavage by specific proteases to release the active peptide. To control this proteolysis the precursor proteins are often kept physically separate from their associated proteases.

A large variety of AMPs exist and this variety can be generated in various ways. In some cases, the same precursor protein is cleaved by different proteases to form different AMPs. Alternatively, short peptides can be fused and cyclised in different combinations to produce a range of AMP products.

Bacteria have several mechanisms for defending themselves against AMP attack:

1. They can modify their cell surface to inhibit AMP binding
2. Inactivate and cleave AMPs by producing proteases and binding proteins
3. Expel AMPs using multi-drug efflux pumps

Bacteria produce their own AMPs so as to reduce competition from other bacteria. These are known as bacteriocins and lantibiotics and can be broad or narrow spectrum depending on the source organism. Commensal bacteria have evolved complex protective mechanisms to avoid killing by host AMPs.

Inappropriate generation of AMPs is now thought to play a role in some immune-mediated inflammatory conditions such as arthritis and Crohn's disease.

AMPs may be useful as novel therapeutics as they are broad spectrum and do not appear to induce significant antibiotic resistance. However, the immunomodulatory effects of AMPs may make them potentially harmful. Alternative strategies would be to target the bacterial response to AMPs.

Further Reading

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